# Cancer Risk Assessment of Extremely Low Frequency Electric and Magnetic Fields: A Critical Review of Methodology

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This review provides a discussion of cancer risk assessment methodology pertinent to developing a strategy for extremely low frequency electric and magnetic fields (EMF). Approaches taken for chemical agents or ionizing radiation in six key topic areas are briefly reviewed, and then those areas are examined from the perspective of EMF, identifying issues to be addressed in developing a risk assessment strategy. The following recommendations are offered: 1) risk assessment should be viewed as an iterative process that informs an overall judgment as to health risk and consists of a complex of related activities incorporating both positive and negative data, tumor and non-tumor end points, and human and nonhuman sources of information; 2) a hazard identification resulting in a conclusion of weak or null effects, such as may be associated with EMF, will need to assign significant weight to animal cancer bioassays conducted under defined exposure conditions as well as to human epidemiologic studies; 3) a default factor to account for possible age differences in sensitivity to carcinogenesis should be included in an EMF risk assessment; 4) lack of evidence of dose response and the apparent lack of DNA reactivity of EMF suggest that a safety (or uncertainty) factor or margin of exposure type of risk characterization may be most appropriate; and 5) an EMF risk assessment should permit at least tentative conclusions to be reached as to the limits of carcinogenic risk from exposure to EMF, and should also define an efficient research agenda aimed at clarifying uncertainties appropriate to a more complete assessment. *Key words*: carcinogenesis, electric fields, EMF, health effects, magnetic fields, risk assessment, toxicology. *Environ Health Perspect* 106:701–717 (1998). [Online 19 October 1998]
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Efforts at assessing all or portions of the existing database of information relevant to the possible carcinogenic potential of electric and magnetic fields (EMF) have generally concluded that there is a lack of consistent evidence of human cancer risk from environmental exposures (*1–4*). These analyses have relied primarily on the large existing database of epidemiologic studies. As these groups point out, because of difficulties in assessing exposures, potential bias and confounding, as well as the inconsistency of epidemiologic studies, much uncertainty remains. Recent animal studies point to the possibility that EMF, though most likely nongenotoxic (*5–7*), may have some potential to enhance the development of neoplasia [reviewed by the National Research Council (NRC) (*2*) and McCann et al. (*8*)]. These promotion studies are currently undergoing independent replication (*9*). In the next few years, results from other carcinogenesis bioassays in animals [see McCann et al. (*8*) for recent review], as well as from new epidemiologic and *in vitro* studies are also expected to become available. With such a comprehensive database available, it should be possible to conduct a more definitive analysis of the carcinogenic potential of EMF. In the United States (*10*) as well as internationally (*11–13*), programs are now in place that have the goal of using these data to develop comprehensive health risk assessments for EMF.

Risk assessment encompasses a wide array of techniques that should be helpful in organizing the complex database on EMF for maximal utilization in a comprehensive and, hopefully, definitive health risk assessment. However, there are aspects of both the emerging biological effects profile and the exposure characteristics of EMF that raise unique problems for risk assessment. To our knowledge, there has been no comprehensive discussion of risk assessment methodology as it might be applied in a broad context to health effects data on EMF.

There is no definitive general method available for risk assessment. Though efforts to achieve scientific consensus on general principles for cancer risk assessment have been common [e.g., (*14*)] and risk assessment has been routinely used in conjunction with regulatory decision making for some years [see the historical review by Albert (*15*)], methods have never been consistently applied among the various regulatory agencies in the United States (*16*),

nor have the same approaches been taken in different countries (*17–20*).

In the United States, the EPA has taken a lead role in developing and implementing cancer risk assessment procedures on a large scale. The agency formally adopted a risk assessment procedure in 1986 (*21*), which has become the standard of comparison in the field. However, over the past 10 years, a body of knowledge has accumulated that has precipitated an intensive reexamination of such so-called standard procedures. This new knowledge primarily involves changing ideas about cancer mechanisms, particularly about what is rate-limiting in carcinogenesis that may be subject to influence from environmental exposures; increasing awareness of the ubiquity of chemical carcinogens in the natural as well as the man-made environment; and increasing understanding that a significant number of cancer-causing substances do not interact directly with DNA.

National debate on the place of risk assessment in regulatory decision making has led to a congressionally mandated Commission on Risk Assessment and Risk Management (*22*), to reexamination of risk assessment procedures by a Committee of the NRC on Science and Judgment in Risk Assessment (*23*), and to the recent release of a proposed revision of cancer risk assessment guidelines by the EPA (*24*). All of these efforts advocate less emphasis on standard default procedures, a substantive role in risk assessment for a much wider range of data sources than in the past, and less reliance on quantitative risk estimates using highly uncertain dose–response extrapolation procedures. These reports are benchmark efforts around which reformulations of government mandated approaches to risk assessment are likely to coalesce in the next few years.

It is our aim to contribute to these discussions, focusing on scientific issues relevant to assessing potential cancer risk from

exposure to EMF. We discuss six key topic areas: 1) variability between different human populations or individuals; 2) extrapolation between animals and humans; 3) the choice of an appropriate dose metric; 4) dose–response assessment and risk characterization; 5) the use of nontumor response data in risk assessment; and 6) the uses of epidemiology in risk assessment. [Exposure assessment, an area critical to developing a risk assessment strategy for EMF, is not addressed in this review. For recent discussion of this topic, see Bracken et al.,_(25).] In a concluding section we offer several general recommendations that may help to guide the selection of risk assessment strategies for EMF.

## The Issue of Uncertainty and the Selection of Defaults

The subjective nature of risk assessment has increasingly come under scrutiny. While both the NRC Committee on Science and Judgment in Risk Assessment (23,26) and the EPA, in their newly proposed guidelines (24), stress the importance of conveying the sources and, where possible, the amount of uncertainty in each risk analysis, of greatest concern are errors that do not have a statistical basis and are due to a limited understanding of carcinogenic mechanisms and biological processes. Though some techniques for dealing with this type of uncertainty do exist (27–31), they are inherently limited because, until greater understanding of carcinogenic mechanisms emerges, criteria used by these techniques to assign certainty and plausibility are themselves subject to uncertainty.

The traditional approach for dealing with uncertainty without a statistical basis is to use so-called defaults, as originally suggested in 1983 by the NRC (32). The EPA has consistently relied heavily on the use of defaults, although other organizations use them either not at all or sparingly, relying more on general principles of analysis and expert consensus (17,33,34). While the recent NRC Committee on Science and Judgment in Risk Assessment recognized the necessity of using defaults, they criticized earlier practices, suggesting that increased attention be given to more precisely identifying and providing scientific and policy justifications for each default and for criteria guiding departures from defaults (35,36).

Thus, an initial area of focus in developing a risk assessment strategy for EMF will be first to determine the degree to which the analysis will rely on the use of defaults and, second, to select and define default options considered necessary. We discuss below three general areas where the adoption of defaults for EMF may be needed.

## Variability between Different Human Populations or Individuals

Interpopulation or interindividual variability includes differences such as increased sensitivity of children and the aged as compared to healthy adults, differences between men and women due to hormonal factors, and differences due to the apparently wide distribution of genetic polymorphisms in a variety of traits that affect sensitivity to carcinogenesis (37–40).

Interpopulation or interindividual differences in sensitivity to EMF are not well documented. For example, laboratory studies to determine whether some individuals are unusually sensitive to the presence of electromagnetic fields have produced conflicting results [reviewed by Knave (41)]. However, interindividual variation in sensitivity to chemical agents is well documented (42,43), and there is no reason to believe that analogous differences do not exist for EMF. This inference is supported by several lines of suggestive evidence. First, epidemiologic studies reporting a positive association between EMF surrogates and leukemia suggest that there may be greater sensitivity among children [for review see NRC (2) and Kheifets and Kelsey (44)]. Second, it has been suggested that EMF may act through a receptor-mediated mechanism [see Kavet (45) for review] and may under certain conditions stimulate cell proliferation. Because genetic polymorphisms in cellular processes such as the control of cell proliferation and affinity differences of receptors involved in receptor-mediated carcinogenesis of agents such as TCDD, estrogens, and peroxisome proliferators have been observed (46), it is not unlikely that if a receptor-mediated mechanism is established for EMF, similar interindividual differences may exist. And, third, blood levels of melatonin vary greatly among different individuals (47), and suggested effects of extremely low frequency (ELF) electric or magnetic fields on the production of melatonin in experimental animals are the basis for a hypothesis (48), albeit uncertain (49–53), that reduced melatonin levels resulting from exposure to EMF may promote cancer in exposed individuals.

Should it be determined that use of a default assumption for interindividual/interpopulation variability is warranted for EMF, there is precedent for its use in regulatory practice. In the past, the primary use of interindividual/interpopulation defaults has been in conjunction with the regulation of noncarcinogens, and the magnitude of default factors used offers some precedent to assist in the selection of a default factor for EMF. For many years, regulatory agencies

using a margin of safety (MOS) approach to regulate noncarcinogens have routinely used a 10-fold uncertainty factor to account for intraspecies variation [reviewed by Johannsen (54)]. There is some experimental support for the magnitude of this uncertainty factor from laboratory studies with inbred rodent strains (55). However, differences in sensitivity to specific agents can vary over a much larger range (56), thus emphasizing the importance of better understanding the magnitude of possible interindividual or interpopulation differences in sensitivity to EMF effects.

Recently, the NRC Committee on Science and Judgment in Risk Assessment (23) recommended that default assumptions to account for interindividual variation be included in cancer risk assessments. In its proposed guidelines (24), the EPA recommended the inclusion of a default uncertainty factor of 10-fold to account for interindividual variation in sensitivity for those carcinogens assessed by a margin of exposure (MOE) risk characterization approach, but not for carcinogens assessed using quantitative extrapolation below the observable dose–response range. Thus, following the proposed EPA protocol, a default uncertainty factor of 10-fold would be appropriate to apply in an EMF risk assessment, provided an MOE type of risk characterization approach is chosen. (See the section on Dose–Response Assessment and Risk Characterization for further discussion on choosing a risk characterization approach for EMF.) Should sufficient information be available to conduct a risk analysis based on data from sensitive subgroups such as children, a default factor would not be necessary.

## Extrapolation between Animal Cancer Tests and Humans

Traditionally, long-term bioassays in rats and mice have played an important role in risk assessment, secondary only to epidemiologic studies. Because epidemiologic studies linking EMF exposure to human cancer are generally considered not to be definitive (2), the results of animal cancer tests conducted under controlled laboratory conditions and over a wide range of exposure conditions are likely to be important in a risk assessment of EMF. The results of a number of such studies will soon be available [see McCann et al. (8) for review]. Therefore, in developing a risk assessment strategy for EMF, it will be important to consider the degree to which new developments in risk assessment may affect assumptions made as to the qualitative and quantitative predictivity of animal tests for results in humans and whether the unique features of EMF require specific attention.

A basic assumption in hazard assessment is that long-term bioassays in rats and mice are valid tests that provide reliable and relevant information concerning carcinogenic potential in humans [see Tomatis et al. (57) for review)]. Recently, however, largely as a consequence of the analysis of a large database of animal cancer test results produced by the National Toxicology Program (NTP), observations have pointed to complexities in the results and stimulated questions regarding the predictive value of long-term bioassays in rats and mice (58–62). On the one hand are concerns (see Dose–Response Assessment and Risk Characterization) regarding possible artifacts due to the use of very high, near toxic doses [(i.e., the maximum tolerated dose (MTD)]. On the other hand, few chemical carcinogens have been observed to induce cancer at doses considerably below the MTD (63,64), and tests conducted at such doses have traditionally not been considered valid predictors of human carcinogenesis because of the statistical insensitivity of animal bioassays [see EPA (21,24) for general discussion].

Most animal cancer tests of EMF are being conducted at magnetic field exposure levels far below those that would correspond to an MTD (although at levels 100–10,000 times the exposure levels suggested as possibly carcinogenic by some epidemiologic studies) (3,8). This is a unique situation. On the one hand, the use of such doses obviates the need to consider uncertainties associated with positive results obtained at near toxic doses. On the other hand, if results of such tests are negative, concerns about the predictive value of animal tests conducted at doses far below toxicity will need to be addressed in considering the relevance of these results to human risk.

A second factor that will need to be considered is the choice of an appropriate methodology for translating quantitative results of animal cancer tests of EMF (whether it be a potency calculated from a positive test or a less than potency value determined from a negative test) to expected results in humans.

Because ELF electric and magnetic fields are physical agents, it may be of interest to examine whether extrapolation procedures that have been used to predict carcinogenic effects of ionizing radiation in humans from results in animals might find application for EMF. Methods that have been used to extrapolate between animals and humans for ionizing radiation [reviewed by the NRC (65) and Storer et al. (66)] are quite different from the default methods commonly used for chemical carcinogens. Two methods that may be useful to consider in developing a

species scaling methodology for EMF are the use of scaling factors based on differences in lifespan (67) or direct extrapolation with no scaling factor using a relative risk model (66).

Species scaling factors most commonly used in carcinogenic risk assessments of chemical agents are based on empirical evidence primarily involving pharmacologic considerations (68–72). These methods use the basic equation

$$Y = aW^n \qquad (1)$$

where $a$ and $n$ are associated with the biologic function $Y$, and $W$ refers to body weight. In the case of carcinogenesis, $Y$ may be any measure of potency, such as the applied dose (usually expressed as milligrams per kilogram per day) of carcinogen required to induce a particular tumor incidence. The superscript $n$ may correspond to assumptions regarding the proportionality of potency to either body weight ($n = 1$), surface area ($n = 0.67$), or metabolic rate ($n = 0.75$).

It is clear that pharmacologic criteria that have been used to develop default interspecies scaling factors for chemical toxicants are not appropriate for EMF. However, pharmacologic criteria such as blood concentration may have some analogy in the extensive studies that have been conducted to determine currents induced in various body areas of different species by externally applied electric fields (73,74) (see The Choice of an Appropriate Dose Metric for further discussion). In fact, Equation 1 has been used to scale short-circuit currents produced by externally applied electric fields between species, using the criterion of equivalency in effective surface area (75), where effective surface area takes into consideration the erectness of posture when scaling between species. The internal current density induced by a vertically polarized external electric field acting on the body surface of grounded humans is 3.7–4.7 times greater than the internal current density due to the same external field acting on a rat (74). Again, with some analogy to the pharmacokinetic distribution of chemicals, anatomically detailed models of various species reveal great differences in induced currents in different parts of the body. For example, in humans and rats exposed to vertical 60-Hz, 10-kV/m electric fields, the axial current densities in the neck and ankle, respectively, are 550 and 2,000 nA/cm², a 3.6-fold ratio (human), and 40 and 1,100 nA/cm², a 27.5-fold ratio (rat) (74). Thus, for externally applied electric fields, the species scaling factor will vary depending upon which body part is of interest.

Species scaling considerations also apply for currents induced by externally applied magnetic fields (74). Magnetic fields induce different electric currents in the tissues of humans and animals because of differing body size and shape. The actual scaling factors depend upon the electrical properties of the tissue in question and the specific details of the anatomical model. The accuracy of the calculated scaling factors also depends on the effectiveness and validity of the computational model employed. For 60-Hz magnetic fields, typical calculations indicate that the average induced currents are about five times greater in humans than in rats for the largest current loop in the torso. A current scaling ratio of about 10:1 is calculated for humans and mice. For recent examples of such calculations, see Xi et al. (76) and Xi and Stuchly (77). Thus, species scaling factors will vary depending on whether electric or magnetic fields are employed.

In developing species scaling factors for EMF, it will also be important to take into account the fact that the same scaling factors will not accommodate all proposed mechanisms of action. Thus, factors based on induced currents will not be suitable if biological effects are believed to be due to direct coupling mechanisms (not involving induced electric fields) such as magnetic field effects on the rate of radical pair recombination, magnetic field coupling to magnetite, or the interaction of magnetic fields at certain hypothesized resonance frequencies affecting either calcium ion movement through membranes or calcium binding to proteins.

## The Choice of an Appropriate Dose Metric

In the field of chemical carcinogenesis, the most commonly used default dose measure for oral exposures is the lifetime average daily potential dose, in milligrams per kilogram body weight. Potential dose is defined as the amount of substance ingested, inhaled, or applied to the skin. It is thus subtly distinguished from applied dose, which is the amount of substance at an absorption barrier, i.e., actually available for absorption (78). The lifetime average daily dose metric does not take into account dose-rate effects, which as the EPA points out (24) could be significant, especially for short-term, high exposure scenarios. However, in the absence of data to the contrary, the EPA suggests use of this default average daily dose metric. Because chemical carcinogens must be absorbed, and many are metabolically processed prior to reaching the target tissue, two other dose metrics may also be used, provided adequate data are available. As defined by the EPA (78), these are internal dose (the

amount of agent crossing an absorption barrier through uptake processes) and delivered dose, or biologically effective dose (the amount of agent available for interaction with a target organ or cell, often stated as the concentration of the agent in the target tissue). The determination of these more refined measures of dose for chemical carcinogens is a major area of research and discussion that has been addressed by the development of various physiologically based pharmacokinetic models (79–81).

In contrast to chemical agents, the choice of a dose metric, or metrics, for EMF effects is complicated both by the biophysically complex nature and variety of EMF and by the variety and uncertainty of experimental evidence linking any direct measure of EMF to biological effects associated with carcinogenesis. Below, we discuss each of these aspects as they relate to the selection of dose metrics for EMF.

*Biophysical aspects.* Although the physical techniques for measuring EMF are well developed, adequate characterization of EMF in biological systems is complex (74,82). Power frequency EMF of 50 Hz or 60 Hz have both an electric field component (usually measured as field strength, in volts per meter) and a magnetic field component [usually measured as flux density, in tesla (T) or gauss (G; $1T = 10^4$ Gauss)]. The concept of electric field describes the force exerted by charged particles. Magnetic fields are associated with moving electric charges, most commonly electric currents. Since both electric field strength and magnetic field flux density are vectors, their complete description requires that direction as well as magnitude be specified. Furthermore, depending on the phase angles of dimensional components, fields can either be linearly or elliptically polarized. In addition, typical power-frequency fields consist not only of the fundamental frequency components at 50 or 60 Hz but also of additional components called harmonics at frequencies that are integral multiples of the fundamental frequency.

With some analogy to the stratification of dose metrics used for chemical agents (potential, applied, internal, and delivered), EMF may be measured as unperturbed external, surface, or internal fields. Unperturbed external fields are unperturbed by the presence of the biological target system; that is, they are measured or calculated without the subject present. Surface fields can be defined functionally as fields that are at the exterior surface of the body. Surface electric fields primarily act on the body surface and are on the same order of magnitude as unperturbed electric fields. Surface electric fields penetrate into living tissue but at tremendously reduced

intensities. Magnetic fields are largely unperturbed by the presence of biological objects, so that both a surface magnetic field and internal magnetic field have the same magnitude as the external magnetic field. Internal electric fields are due to effects of both the external and surface electric fields and magnetic fields. Compared to the unperturbed external electric field, the electric field strength inside the body is reduced by a factor ranging from 10,000 to 1 million depending on the geometric configuration of the body area measured. For example, using human

models exposed to a 10-kV/m field at ground level directly under a 765-kV transmission line, internal fields of 0.7–54 mV/m have been measured (73). Static magnetic fields (such as those present at the surface of the earth) do not induce electric field currents as long as the body and the static field source are stationary relative to one another. (Normal body motion in the presence of a geomagnetic field induces currents and voltages comparable to those induced by a 1 µT 60-Hz field.) Time-varying magnetic fields [such as sinusoidal alternating current (AC) fields]

**Table 1.** EMF effects on biological systems considered to be credible by the National Research Council (NRC) Committee on Possible Health Effects of Exposure to Residential Electric and Magnetic Fields[a]

| Biological effects | Exposures cited by the NRC | Comments |
|---|---|---|
| Human epidemiologic evidence, residential exposure | Wire-code configuration | The committee concluded that results of studies using direct field measurements were equivocal or negative |
| *In vitro* studies: specific features in cellular signal-transduction pathways Changes in ODC activity[b] | ≥100 µT[c] | Effects on other signal transduction-related events (except changes in calcium, which is discussed separately) were not considered by the committee to be independently replicated |
| Changes in intracellular calcium concentration | >50 µT[d] | The committee indicated that only experiments on thymic lymphocytes in which Con-A stimulated cells showed a change in calcium transport met independent reproducibility requirements |
| *In vivo* evidence of effects in humans or animals Mammary cancer in rats | ~100 µT[e] | Several reports from the same laboratory suggest an increase in breast cancer incidence in rodents pretreated with the carcinogen dimethylbenz(a)anthracene; the committee emphasizes that these studies have not been independently replicated |
| Behavioral responses | ≥5 kV/m | The committee emphasizes that neither the detection of electric fields by animals or humans nor observed behavioral effects are considered adverse; data supporting behavioral effects from exposure to AC magnetic fields are considered uncertain |
| Inhibition of nighttime pineal and blood melatonin concentrations in animals | 10 µT– 5.2 mT | The committee considers that the magnetic field studies are suggestive, but that the electric field studies are not compelling |
| Bone healing responses in animals[f] | >0.5 mT, pulsed[g] | Widely used clinically; possible adverse effects have not been reported, nor have they been systematically studied |

Abbreviations: ODC, ornithine decarboxylase; Con-A, concanavalin A; AC, alternating current.
[a]Except as indicated, Table 1 reflects the summary judgment of the NRC Committee on the Possible Health Effects of Exposure to Residential Electric and Magnetic Fields (2) as expressed in the executive summary of that report; the committee also concluded that there was no convincing evidence of genotoxic effects, effects on reproduction or development, or effects on gene expression and protein synthesis from exposure to ELF fields.
[b]Based on the committee's discussion in the body of the report, we have inferred that the "specific feature" referred to in the executive summary is changes in ODC activity.
[c]This value was reported in the executive summary of the NRC report. In the body of the report, the conditions under which the two studies discussed as providing credible evidence of effects on ODC activity were conducted were 0.1 mV/cm (152) and 60-Hz, 10 µT (153).
[d]This value was reported in the executive summary of the NRC report. In the body of the report, three studies were listed as meeting independent reproducibility requirements; two of these, Walleczek and Budinger (154), in which statistically significant effects were detected using a 3-Hz pulsed magnetic field with peak flux densities at 6.5 or 28 mT, and Yost and Liburdy (155), in which effects were detected using a 16-Hz, 42.1 µT magnetic field with co-linear static magnetic field of 23.4 µT, appear in Table A3-2 in the committee report.
[e]The executive summary did not include an exposure level; the value reported is from Löscher et al. (91).
[f]The committee did not evaluate bone healing in humans.
[g]This value was reported in the executive summary of the NRC report; the conditions under which the studies evaluated by the committee were conducted were 0.1–15 mT, 1–100 mA/cm².

generate their own electric fields internally in biological systems through magnetic induction, according to Faraday's Law. These internal fields result in induced currents termed eddy currents. Induced currents are measured in milliamps per square centimeter $(mA/cm^2)$. Currents induced by most environmental exposures to magnetic fields are believed to be smaller than currents that are endogenously present in the body (82).

It should be clear from the above discussion that the determination of magnetic flux density inside the body is straightforward because it is equal to the external flux density. However, the determination of electric field strength inside the body is complex since it represents the combined effect of external and surface electric fields as well as induction by magnetic fields.

A variety of dose metrics have been suggested for EMF, most commonly measures related to field strength such as time-weighted average field strength, time exposed to field strengths above a certain threshold level, time exposed to field strengths within certain intensity windows, or the rate of change of field intensity. Other measures such as the frequency and intensity of switching transients or measures that are restricted to certain frequency windows have also been discussed [e.g., see Morgan and Nair (83)]. The fact that several studies examining correlations between various dose metrics based on field strength have produced weak or variable results (84–88) underlines the importance of the proper selection of a biologically relevant dose metric to define dose–response relationships (89).

*Biological aspects.* The primary difficulty in selecting a dose metric for EMF is that the biological effects database does not present an adequate or consistent picture. The experimental literature on biological effects of EMF is enormous. Various aspects of this literature have frequently been reviewed. It is not our intention to evaluate this literature. Recently, an expert committee of the NRC completed an extensive critical evaluation of a large part of the EMF biological effects literature (2), and a brief examination of the studies considered by the NRC to be credible (see Table 1) will make it clear that neither an adequate nor a consistent picture is presented.

First, surrogate measures of exposure have been used in many residential epidemiologic studies that are only weakly correlated to direct measurement of ELF electric and magnetic field parameters. The NRC committee concluded that, in the aggregate, studies indicating a positive association which used direct present-day measurement of EMF were not convincing. The only residential epidemiologic studies considered by the committee to demonstrate a consistent effect used wire-code configurations as a surrogate. Wire-code configurations may also serve as surrogates for a number of environmental factors unrelated to EMF [reviewed by the NRC (2)].

Second, there is a lack of directly relevant or independently replicated *in vivo* animal carcinogenesis data that can be used as the basis for the selection of a dose metric. Although several long-term chronic bioassays in which EMF exposure is being carefully monitored are in progress [see McCann et al. (8) for recent review], there are currently no adequate data from such studies that demonstrate either the presence or absence of a carcinogenic effect of EMF. Furthermore, carcinogenesis promotion studies involving mammary cancer in rats that suggest an increase in tumor incidence with increasing flux density (90,91) have not been independently replicated.

Third, some biological effects of EMF involving nontumor end points considered by the NRC to be credible (such as behavioral responses) have no apparent relationship to cancer.

Fourth, tissue, biochemical, or hormonal changes produced by EMF that may be related to carcinogenic processes have not been clearly linked to adverse health effects, nor is there any unique set of field parameters that have been observed to produce these effects. Some biological effects of EMF involving certain nontumor end points could affect carcinogenic processes and might therefore serve as indicators of possibly relevant dose metrics. Examples in Table 1 are effects on melatonin, signal transduction-related pathways, particularly ornithine decarboxylase (ODC) activity, and calcium movement. Data not included in Table 1 also suggest that, under certain conditions, sinusoidal magnetic fields may stimulate cell proliferation *in vitro* (2,92). However, very different exposure parameters have been observed to produce these effects (see Table 1 footnotes).

Thus, based on the analysis of the NRC committee (2), an adequate biological basis for selection of a dose metric for EMF does not exist at present. In spite of the lack of convincing data demonstrating carcinogenic or related effects in biological systems, some attempts have been made to elucidate the shape of dose–response curves using actual biological effects data and various dose metrics. For example, Juutilainen et al. (85) used epidemiologic data on early pregnancy loss and several dose metrics based on field strength, and tested the goodness of fit of these data using several dose–response models. While of some methodological interest, such studies contribute little to the selection of a dose metric because the biological effects data used were not statistically significant or independently replicated. Thus, the absence of a biological basis for the selection of a dose metric, combined with the variety of options for dose metrics offered by the biophysical complexity of EMF, indicates that it will most likely be necessary to adopt a set of default dose metrics for risk analysis. If definitive evidence of biological effects relevant to carcinogenesis becomes available, those data should provide a basis for establishing preferred options. If such data are not available, regulatory interest (e.g., widespread exposure or concerns about occupational exposures) or the feasibility of exposure determination (e.g., the availability of instrumentation and methodology for measuring personal time-weighted average magnetic field exposures) may guide the selection of defaults.

## Dose–Response Assessment and Risk Characterization

The outcome of a dose–response assessment is almost always some measure of potency. Examples of potency descriptors that have commonly been used for chemical agents are shown in Table 2. These potency descriptors include nonextrapolated measures, relative potency descriptors, and extrapolated measures. The use of a nonextrapolated measure of potency is consistent with a safety (or uncertainty) factor approach to risk characterization. The use of an extrapolated measure of potency is commonly applied in conjunction with the calculation of risk from extrapolated slope values and environmental exposures of interest. Several examples of these two general approaches to risk characterization that have been used for chemicals are in Table 3.

From a regulatory standpoint, whether or not a potential carcinogen is considered to be genotoxic or to interact directly with DNA can have a significant bearing on whether a safety factor or low-dose extrapolation risk characterization is employed. Scientific justification for the application of this criterion is uncertain and complex, and approaches taken among different regulatory bodies vary. Because the preponderance of evidence indicates that EMF are not genotoxic and do not appear to interact directly with DNA [see McCann et al. (6) for recent review], it will be important to understand this criterion and how it may be applied in selecting a risk strategy for EMF.

While some countries do not use a criterion of genotoxicity or DNA reactivity to select a risk characterization approach (18), other countries such as the Netherlands (93) have used this criterion for some time. In such cases it is usually assumed, despite uncertainty [see Barrett (94) for discussion], that nongenotoxic

**Table 2.** Potency descriptors[a]

| Approach | Definition | Comments | References |
|---|---|---|---|
| **Nonextrapolated measures** | | | |
| NOEL, NOAEL, or LOAEL | The highest dose tested for which either no effect (NOEL) or no adverse effect (NOAEL) is observed, or the lowest dose tested for which an adverse effect was observed (LOAEL) | Traditional methods used to describe toxicity of agents believed to have a threshold mechanism of action; used in some countries outside the United States for nongenotoxic carcinogens | (17,54,93,156) |
| $LED_{10}$ or $LED_{01}$ | The lower 95% confidence limit on a dose associated with 10% ($LED_{10}$) or 1% ($LED_{01}$) risk; termed the "benchmark" dose estimation method | Proposed for use by the EPA to estimate a point of departure for extrapolation; not model dependent; any dose–response model that fits the experimental data may be employed | (24,157,158) |
| BESTNOEL | Biologically evaluated, scientifically tested NOEL; the inflection point in the marginal response curve between the absence of an observable biological response and an observable relevant biochemical response | Suggested as a method for accommodating noncancer data in cancer risk assessment | (123) |
| $TD_{50}$ | Chronic dose rate that would induce tumors in half of the animals which would have remained tumor free at zero dose over the standard life span for the species | Used to describe results of over 4,000 animal cancer bioassays comprising the database accumulated by the NTP carcinogenesis testing program as well as experiments from the published literature | (159–161) |
| Doubling dose | Chronic dose required to double the spontaneous cancer (or mutation) rate | Commonly used in genetic risk assessment and in conjunction with short-term genotoxicity assays | (65,162,163) |
| **Comparative potency descriptors** | | | |
| Relative biological effectiveness (RBE) | The ratio of doses of two different types of radiation required to produce the same effect. In radiation biology, usually expressed relative to a standard LET (linear electron transfer) value | Used for many years in radiation biology; a related approach (relative potency) has been suggested for use with EMF | (65,115,116) |
| Toxicity equivalence factors (TEFs) | A relative measure of toxicity determined by dividing an observed potency value for a substance of interest by the potency for a related substance, which is used as a standard reference | Developed by the EPA for use with chemical groups such as dioxins, PCBs, and PAHs, which are structurally related and believed to act through the same mechanism but for which adequate carcinogenesis data may only exist for one or a few members of the group | (164–166) |
| **Extrapolated measures** | | | |
| Calculation of a slope factor— e.g., cancer incidence per lifetime average daily dose | Maximum likelihood estimate (MLE) or 95% upper confidence limit (UCL) of the linear slope term estimated from animal cancer test dose–response data using the LMS (linearized multi-stage model).[b] Termed the "q-one-star" by the EPA | Standard procedure employed by the EPA in their 1986 guidelines; also routinely used by the Consumer Product Safety Commission | (16,21,54) |
| | The projected slope (analogous to q-one-star) calculated from a straight line drawn to zero from the $LED_{10}$ | Proposed for use by the EPA when evidence is not indicative of a nonlinear dose response | (24) |

Abbreviations: NTP, National Toxicology Program; EMF, electric and magnetic fields; PCBs, polychlorinated biphenyls; PAHs, polycyclic aromatic hydrocarbons.
[a]This is not an exhaustive list, but it should demonstrate the variety of approaches that have been applied.
[b]A variety of mathematical models are available for estimating extrapolated slope values, including linear, mechanistic (e.g., multihit, multistage), tolerance distribution (e.g., Weibull, Gamma-multihit), time-to-tumor (e.g., lognormal, Armitage-Doll), and biologically motivated models (e.g., Moolgavkar-Knudson) [for review, see (54)].

mechanisms are reversible, resulting in dose–response curves characterized by a threshold [e.g., see Whysner and Williams (18)], and that genotoxicity mechanisms are irreversible, resulting in dose–response curves characterized by linearity at low doses (95,96). If a threshold mechanism is believed to apply, a safety factor risk characterization approach is chosen. If a nonthreshold mechanism applies, a low-dose extrapolation procedure is used.

Until recently, the EPA has reserved the use of safety factor approaches for noncarcinogens (see examples in Table 3) and has used a low-dose extrapolation approach for all carcinogens, regardless of whether there is evidence for genotoxicity or DNA reactivity (21). In their newly proposed guidelines, the EPA has modified this position. They have proposed an approach in which evidence for "gene mutation due to DNA reactivity" is

used as a means of determining whether risk characterization approaches involving a default linear dose–response extrapolation or a default MOE/MOS approach will be used (24). If there is evidence supporting DNA reactivity, the EPA proposes to use the former approach. In the absence of such evidence, the latter safety factor approach is proposed, provided there is additional evidence supporting a nonlinear mode of action. In the

**Table 3.** Risk characterization approaches

| | | | |
|---|---|---|---|
| The calculation of risk from extrapolated slope values (such as $q_1^*$) and environmental exposures of interest | Excess individual lifetime risk [the product of $q_1^*$ and an exposure (in mg/kg body weight per day) of interest] $10^{-6}$ *risk* (the dose corresponding to a particular level of individual lifetime risk, in this case $10^{-6}$) Population risk (the excess number of cancers in an exposed population, the product of individual risk, and the total number of individuals at risk) Unit risk (excess lifetime risk due to continuous constant lifetime exposure of one unit of carcinogen concentration); primarily used by the EPA for air contaminants | Used extensively in the United States | (21,167) |
| Safety, or uncertainty factor approaches | | | |
|   Margin of exposure (MOE) | The ratio of a minimum dose value corresponding to a carcinogenic response (the EPA suggests the $LED_{10}$) to the dose corresponding to an environmental exposure of interest | In their newly proposed guidelines, the EPA has proposed this approach for carcinogens with nonlinear dose–response curves | (24) |
|   Human exposure/ rodent potency (HERP) | The percentage of the rodent potency ($TD_{50}$) received by a human during a given lifetime exposure | Used to rank animal carcinogens based on human exposure; similar in concept to the MOE and essentially its inverse | (168,169) |
|   Margin of safety (MOS) | A general approach indicating the use of safety or uncertainty factors rather than extrapolation | | (54,156,172,173) |
| | ADI (acceptable daily intake), the daily intake of a chemical which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at the time | Used by the FDA in conjunction with noncarcinogenic toxicants in food, but has also been suggested for use with carcinogens (170) | |
| | RfD (reference dose) or RfC (reference concentration), estimates of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime | Calculated by dividing the NOAEL or LOAEL by a set of uncertainty factors to account for inter- and intraspecies differences (100-fold), lack of chronic data (10-fold), use of a LOAEL instead of a NOAEL (3- to 10-fold), data quality and completeness (3- to 10-fold), and a discretionary modifying factor for other miscellaneous uncertainties (1- to 10-fold)[a] | |

Abbreviations: $LED_{10}$, lowest effective dose associated with 10% risk; FDA, Food and Drug Administration; NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level.
[a]For examples of the use of the RfD and RfC, see EPA (171).

absence of such additional evidence, a default linear extrapolation will still be employed.

On the one hand, the EPA's new proposal moves away from risk characterizations based only on default dose–response extrapolations because use of the linearized multistage (LMS) model is no longer recommended, a case-by-case approach to dose–response analysis that may involve biologically based or case-specific extrapolation models is emphasized, and an MOE/MOS approach is accommodated in certain cases (24). [Parenthetically, the NRC Committee on Science and Judgment in Risk Assessment (23) has recommended the continued use of the LMS model.] On the other hand, the proposal by the EPA to use linear low-dose extrapolation as a generic default procedure for dose–response curves without convincing evidence of nonlinearity (24) regresses to

the use of a procedure with even less justificatory evidence than use of the LMS model.

The scientific justification for the use of any default low-dose extrapolation procedure with cancer bioassay data is tenuous. Because of the highly uncertain nature of this approach, the Commission on Risk Assessment and Risk Management (22) recently recommended that a safety factor approach be used for all carcinogens. Scientific justification for the use of a linear extrapolation model, as proposed by the EPA (24), is particularly problematic. First, complexities involved in linking mutagenesis or DNA reactivity to carcinogenic mechanisms and in classifying agents as genotoxic or nongenotoxic have been well documented (42,94, 97–102). Second, it is becoming increasingly evident that a significant number of chemical carcinogens, even some so-called genotoxic carcinogens, may act

primarily through mechanisms which do not involve direct interaction with DNA, thus producing dose–response curves that are not linear, even at low doses (see examples and references in Table 4).

Third, analysis of tumorigenesis dose–response curves from the large database of animal bioassays of chemical agents now available indicates that a significant portion of these curves are more consistent with a quadratic rather than a linear dose– response (103), that some dose–response curves demonstrate saturation (104), that others even demonstrate hormetic effects (30,105,106), and further, that there is no association between DNA reactivity and dose–response curve linearity (103). Such experimental observations may be limited to analysis of test data obtained at near-toxic doses or to the pharmacological aspects of

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**Table 4.** Mechanisms associated with carcinogenesis[a]

| General classification | Mechanisms | Example agents |
|---|---|---|
| **Mechanisms that involve heritable genetic or epigenetic changes** | | |
| Direct interaction with DNA leading to genetic changes[b] | Alkylation<br>Frameshift mutagenesis<br>Clastogenesis | Methyl methanesulfonate, ethylnitrosourea<br>2-Acetylaminofluorene, benzo(a)pyrene<br>Ionizing radiation, metals, benzene |
| Indirect interaction with DNA leading to genetic changes[b] | Gene amplification<br>Aneuploidy<br>Induction of enzymes resulting in metabolic activation of an endogenous or exogenous genotoxic agent | Arsenic<br>Asbestos, DES[c]<br>Aroclor 1254, phenobarbital |
| Heritable epigenetic alteration of gene expression | Interaction with DNA methyl transferase (non-DNA interactive) or DNA methylating agents (DNA-interactive)<br>Transformation of mammalian cells in vitro | Ethionine, 5-azacytidine<br><br>Ionizing radiation |
| **Mechanisms that involve stimulation of cell proliferation** | | |
| Mechanisms associated with cytotoxicity | Physical damage<br>Hepatotoxicity<br>Kidney toxicity<br><br><br>Bladder toxicity<br><br>Stomach toxicity | Skin abrasion<br>Carbon tetrachloride, furan, methapyrilene<br>Chloroform, nitrilotriacetate, unleaded gasoline, perchloroethylene, 1,4-dichlorobenzene, pentachloroethane<br>Saccharin, ascorbate, BHT, BHA, isoleucine, leucine, uracil, terephthalic acid<br>BHA, ethyl acrylate |
| Mechanisms not necessarily linked to cytotoxicity that involve cell proliferation | Inhibition of gap junction intercellular communication<br>Inhibition of apoptosis<br><br>Over-production of TSH, which induces thyroid hypertrophy and hyperplasia<br><br><br><br>Inhibition of hexamethylene bis-acetamide-induced differentiation in murine erythroleukemia cells | Phenobarbital, DDT PCBs, clofibrate<br>Phenobarbital, cyproterone acetate, peroxisome proliferators<br>Low iodine diet or chemicals such as thiouracil, propylthiouracil, and methimazole, which decrease circulating levels of thyroid hormones<br>TPA |
| Receptor-mediated mechanisms | Binding to peroxisome proliferator-activated receptor leading to transcriptional activation of genes coding for peroxisomal enzymes and cell proliferation<br>Binding to the aryl hydrocarbon receptor resulting in altered expression of several proteins, including TGF-α which may bind to the EGF receptor, leading to increased cell proliferation<br>Binding to membrane-bound protein kinase C resulting in events including inflammatory reactions, the induction of ODC, and cell proliferation<br>Binding to estrogen receptors resulting in stimulation of cell proliferation in estrogen-sensitive cells, leading to neoplasia | Wy 14,643, ciprofibrate, diethylhexlphthalate, methyl clofenapate<br><br>TCDD<br><br><br>TPA<br><br><br><br>Some estrogens (ethinyl estradiol, 17β-estradiol), DES[c] |

Abbreviations: DES, diethylstilbestrol; BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisole; PCBs, polychlorinated biphenyls; TSH, thyroid-stimulating hormone; TPA, 12-O-tetradecanoylphorbol-13-acetate; TGF-α, transforming growth factor-α; EGF; epidermal growth factor; ODC, ornithine decarboxylase.
[a]Includes mechanisms associated with any of the three stages of carcinogenesis: induction, promotion, and progression. Mechanisms resulting in neoplasia are not known with certainty; mechanisms listed are those for which significant supporting evidence exists in nonhuman systems. Most of the example agents listed are associated with more than one mechanism; where possible we have listed agents next to the mechanism with which they are most commonly associated. Information in this table was compiled from several sources (42,94,97–99,174–177). The table is not intended to be an exhaustive compilation, but to illustrate the variety of mechanisms associated with carcinogenesis.
[b]Genetic changes include gene mutations, chromosome rearrangements, gene amplification, and aneuploidy; some of these genetic changes, in particular gene amplification and aneuploidy, are not detected by most genotoxicity assays.
[c]Genotoxicity evidence is conflicting.

chemical carcinogenesis. (31,58,107–109). Nevertheless, these observations emphasize the tenuous nature of the evidence supporting the use of generic dose–response models to calculate potencies for chemical carcinogens.

It will be important to consider the relevance of this information to the selection of a dose–response assessment strategy for EMF. As discussed above (see Extrapolation between Animal Cancer Tests and Humans), the data currently considered most convincing regarding the possible carcinogenic potential of EMF appear to suggest an effect at exposures far below those

which elicit acute or subacute toxic effects. Therefore, distortions of dose response due to toxicity are not likely to be a concern for EMF. In addition, some exposures included in a number of completed and ongoing animal cancer bioassays [see McCann et al. (8)] are at or near human exposure levels, thus precluding the need for extrapolation far below the range of observable effects in these cases. However, many exposures included in animal bioassays do significantly exceed human exposure levels, and the issue of dose–response extrapolation will need to be addressed in these cases.

For EMF, it is important to realize that, at least as proposed by the EPA, if dose–response extrapolation is determined to be desirable for EMF data, a default linear extrapolation would be indicated unless a convincing argument for nonlinearity is presented. Therefore, an important area to address in the development of a risk strategy for EMF is the question of whether a convincing argument for the likelihood of a nonlinear dose response can be made.

On the one hand, dose–response curves for EMF effects might be expected to be simpler than those for chemical agents

because electric and magnetic fields are physical agents and would not be expected to be subject to the same homeostatic mechanisms as chemical agents. On the other hand, probably the most compelling argument for the expectation of a nonlinear dose response for EMF is the absence of convincing evidence for any potential to interact with DNA (6). There is also some suggestion in the published literature that EMF may be capable of affecting biological processes such as cancer promotion, induction of ODC, and cell proliferation (see Table 1 and The Choice of an Appropriate Dose Metric). It is not our intention to evaluate these data, which must be considered uncertain unless independently replicated, but to present them as an example that illustrates that there is some evidence, however tentative, for the ability of EMF to enhance cellular processes associated with carcinogenesis that are believed to involve nonlinear mechanisms.

Two additional factors also support the conclusion that a scientific basis for the use of low-dose extrapolation methods in a risk assessment of EMF effects does not exist at this time. First, there are no plausible theoretical hypotheses or experimental biological data suggesting relevant mechanisms of action that could provide a basis for extrapolation. A number of biophysical mechanisms have been proposed to explain the interaction of EMF with biological systems (2,110,111). These include energy coupling mechanisms, such as induced current effects; direct force mechanisms, such as forces on moving ions; mechanisms involving direct force effects on ferromagnetic particles; resonant mechanisms, such as ion cyclotron or parametric resonance; free radical mechanisms; and spatial and temporal signal-averaging mechanisms. All of these theories suffer either from serious theoretical difficulties or a lack of experimental support in living systems at field levels that are likely to be relevant to human exposure (112). It is therefore premature to discuss how any particular theory might suggest a dose–response extrapolation strategy for EMF.

And second, endogenous electric fields in tissues provide a background on top of which induced fields must act to produce effects in intact living organisms (113,114). Endogenous fields, therefore, define a threshold for the possible effects of induced electric fields due to external magnetic or electric fields.

Should adequate data become available, it should therefore be possible to make a convincing case for the use of a safety (or uncertainty) factor type of risk characterization approach, such as an MOE/MOS approach using potency measures similar to

one or more of the nonextrapolated or comparative potency measures in Table 2 to describe tumorigenicity or other relevant nontumor data on EMF. In fact, relative potency descriptors have recently been suggested for use with EMF (115,116). In contrast, neither a scientific nor an empirical basis for the application of low-dose extrapolation procedures to EMF effects data exists, and in fact, such a basis is even less well established for EMF than for chemical agents. It will therefore be important to carefully justify, and delimit, the use of any dose–response extrapolation procedures chosen as defaults for use with EMF effects data.

## The Use of Nontumor Response Data in Risk Assessment

As reinforced by formal sanction given in the EPA's newly proposed guidelines (24), greater emphasis is now being placed on the use of nontumor response data in cancer risk assessment (69,109,117–119). In the EPA proposed guidelines, nontumor response data is accommodated in several ways. First, the concept of hazard identification has been expanded to include all pertinent sources of response data in a more substantive way than in previous guidelines. Such data could include, for example, nontumor response data indicating species specificity or data suggesting a threshold mechanism of action that might preclude extrapolation from the observable range of tumor dose response. Second, the EPA has proposed the use of quantitative response effects preceding tumorigenesis to enhance the analysis of tumor dose response in both observed and extrapolated ranges. Such effects might include, for example, cell proliferation, enzyme induction, or receptor binding. And, third, the EPA has proposed the use of biologically based or case-specific extrapolation models that incorporate nontumor response data, provided their relevance to mechanism is supported by sufficient data.

There are as yet no standard methods of using nontumor response data in quantitative risk assessment. However, as illustrated in Table 5, there are general approaches that may be adaptable to specific cases, depending on the quality and availability of appropriate data. These include 1) measurement of nontumor response parameters for direct use in a mathematical model [reviewed by Thorsland et al. (120) and Cohen and Ellwein (121)]; 2) augmenting information on the likely shape of the tumor dose–response curve at low doses by determining the shape of a dose–response curve for a nontumor end point believed to be correlated with tumorigenesis; 3) identification of threshold doses

required for nontumor effects believed to be prerequisite for neoplasia; 4) measurement of the same nontumor end point in the tissues of different species or sexes to determine relative sensitivities for risk extrapolation; and 5) reconstruction of a tumor dose–response curve using response data for nontumor end points as a dose surrogate.

The five general approaches discussed above, while by no means exhausting the ways in which nontumor response data may be useful in risk assessment, suggest some approaches that may be useful to consider in developing risk assessment strategies for EMF. As discussed previously, several proposed biological effects of EMF involve nontumor end points that could affect carcinogenic processes (see Table 1). These include effects on serum melatonin concentrations, ODC activity, calcium movement, and cell proliferation. These nontumor end points could in principle be incorporated into a risk assessment strategy, provided experimental or theoretical support emerges to provide linkage to an overall mechanism of action of EMF. For example, if a reduction in serum melatonin concentration was considered to occur prior to, and to be a prerequisite for, promotional effects of magnetic fields as proposed by Stevens (122), a minimally effective dose could be determined using methods such as that suggested by Gastel and Sutter (123) (Table 5) or the benchmark dose (BMD) approach recommended in the proposed EPA guidelines (24). The same procedures could be applied using other nontumor response data provided a plausible mechanistic linkage could be constructed.

Other potential applications of nontumor response data for EMF are apparent by analogy with the examples in Table 5. In particular, it should be possible to use such information to aid in determining species sensitivity conversion factors by, for example, comparing the potency of induction of ODC by EMF in rat and human cells in culture, using in vivo rat data to implement a parallelogram approach. In addition, if adequately defined dose–response curves were available for nontumor end points such as ODC induction, in principle, they could be used to augment information on the shape of tumor dose–response curves at low exposures.

## The Uses of Epidemiology in Risk Assessment

Historically, when adequate epidemiologic data have been available, they have assumed a central role in both the qualitative and quantitative aspects of risk assessment [for example, see the EPA's 1986 risk assessment guidelines (21)]. This emphasis on epidemiologic data is reasonable, given its

more obvious relevance to humans than data from nonhuman sources. However, this gain in relevancy is at a cost due to methodological difficulties involved in the conduct and interpretation of epidemiologic studies. A stricter control of experimental conditions is more easily satisfied in the laboratory setting in which most nonhuman experiments are conducted (*124–126*). Thus, whereas uncertainties associated with nonhuman data usually center on interspecies conversion and issues such as extrapolation below the near-toxic doses used in animal studies, uncertainties attendant to the use of human epidemiologic data are often dominated by issues stemming from difficulties in adequately defining exposures and adjusting for potential bias or confounding factors.

In the EPA's recently proposed risk assessment guidelines (*24*) there are two primary changes in the treatment of human epidemiologic evidence: 1) there is greater openness to a variety of uses of nontumor response information in both the hazard assessment and the dose–response assessment phases of risk assessment; and 2) there is increased emphasis on the need to include all epidemiologic studies, both positive and negative, in an overall evaluation of the carcinogenic potential of any agent.

Examples of uses of epidemiologic data in risk assessment that are consistent with these policy changes are described in Table 6 and are discussed below.

1. Application of a range of weighting factors, including quality and causal criteria, to individual studies as part of an overall qualitative weight of evidence hazard assessment. Quality and causal criteria relative to epidemiologic studies have been fully discussed in the literature and we will not address them further here. For recent review see EPA (*24*), Kheifets and Kelsey (*44*), Shore et al. (*124*), Hertz-Picciotto (*127*), and Ahlbom et al. (*128*). The three weight of evidence classifications recently proposed by the EPA (*24*) exemplify an outcome of this type of analysis. According to this new categorization, while evidence from epidemiologic studies demonstrating causality between human exposure and cancer is still required in order to consider that an agent is a "known" human carcinogen, the highest category designation has been expanded to "known/likely" from earlier more restrictive schemes (*21*) so that agents for which epidemiologic studies do not exist or for which epidemiologic evidence is equivocal may still be assigned to the "known/likely" category based on nonhuman data only. Thus, under the EPA's newly proposed guidelines, while

**Table 5.** The use of nontumor response data in cancer risk assessment[a]

| General approach | Examples | References |
|---|---|---|
| Measurement of nontumor response parameters for direct use in a mathematical model of carcinogenesis | The use of data on the rate of formation and size of hepatocellular foci in rats to estimate an initiation rate for DNT. It was assumed that preneoplastic lesions could be represented by γ-glutamyltranspeptidase-positive foci produced in rats pretreated with subinitiation doses of diethylnitrosamine followed by DNT. The number of foci was considered to be related to both the initiating and the promoting potential of DNT, but size of the foci was considered to be related only to the promoting potential of DNT. | (*178*) |
| | The use of data on the shape of the dose–response curve for DNA adducts produced by 2-AAF in mouse liver to justify modeling the effect of 2-AAF on the probability of initiation as linear | (*179*) |
| Augmenting information on the likely shape of the tumor dose–response curve at low doses by determining the shape of a dose–response curve for a nontumor end point believed to be correlated with tumorigenesis | Measurement of the maximal binding capacity of the EGF receptor in liver as a function of TCDD dose to demonstrate that the receptor binding response is hyperbolic at low doses. If binding to the EGF receptor is rate limiting in the neoplastic process induced by TCDD, this result would suggest that cancer risk at doses below the observable range would be higher than predicted by a linear extrapolation from observed tumor responses | (*180,181*) |
| Identification of threshold doses required for nontumor effects believed to be prerequisite for neoplasia | Abrasive silicate crystals resulting from high doses of sodium saccharin in male rats lead to regenerative hyperplasia followed by bladder tumors. Thus, the dose–response curve for precipitation of abrasive crystals may be a more useful end point for assessing cancer risk than extrapolation from tumor dose response. | (*182*) |
| | Determination of a BESTNOEL (minimal effective dose) for CYP1A1 mRNA induction by TCDD. CYP1A1 mRNA induction results from the binding of TCDD to the Ah receptor and is believed to be included in the pathway(s) leading to TCDD-induced neoplasia. The BESTNOEL is several orders of magnitude below TCDD doses that have been observed to result in hepatic carcinomas in rats. | (*123*) |

positive evidence from epidemiologic studies is still important in hazard assessment, the well-known difficulties in definitively establishing causation through epidemiologic studies involving environmental exposures has been taken into account by softening the former absolute requirement for positive epidemiologic evidence in order to assign a potential carcinogenic agent to the highest weight of evidence category. On the other side, a similar expansion in data required to assign a potential carcinogen to the category suggesting noncarcinogenicity ("not likely") has occurred. While "extensive human experience that demonstrates lack of effect" (*24*) will still result in a "not likely" category assignment, appropriate negative evidence from animal studies will also suffice.

2. Application of a meta-analysis and combined analysis of raw data (*124,125,129*).

The procedures usually grouped under this heading include using results from multiple epidemiologic studies in quantitative procedures involving weighting individual studies according to quality criteria and assessing heterogeneity. Results may also include the calculation of a summary risk estimate and new confidence intervals either using summary statistics based on multiple individual studies or using a pooled analysis with raw data. Application of these techniques is not well developed, and some attempts to simply obtain overall risk estimates or confidence intervals by combining summary statistics and the use of subjective quality weighting schemes have been criticized [see, for example, the recent debate in the *American Journal of Epidemiology* (*130–133*)]. Despite difficulties, these techniques offer a systematic approach to identifying potential sources of inconsistency and variability among

**Table 5.** *continued*

| General approach | Examples | References |
|---|---|---|
| Measurement of the same nontumor end point in the tissues of different species or sexes to determine relative sensitivities for risk extrapolation | Histopathological comparison of TCDD toxicity to rat thymus and human thymus grafts in SCID mice.[b] Allows a direct comparison of human and rodent tissue sensitivity to toxic effects of TCDD *in vivo*. | (183) |
| | Comparison of the potency of induction of DNA adducts in mouse and human lymphocytes to obtain a species sensitivity conversion factor.[c] This general approach may be adapted to inform the development of interspecies scaling factors specific to particular agents using any molecular, biochemical, or cellular end points believed to be critical in pathways leading to neoplasia, as long as the end points are measurable *in vivo* or *in vitro* in both rodent and human tissues. | (184) |
| Reconstruction of a tumor dose–response curve substituting a surrogate dose for the administered dose of carcinogenic agent | Application of the LMS dose–response extrapolation model to a reconstructed dose–response curve for formaldehyde in which DNA–protein cross-links are used as a surrogate for administered dose. The use of this dose surrogate more accurately reflects the tissue dosimetry of formaldehyde than does administered dose, and also results in a near 50-fold reduction in estimates of human risk as performed by the EPA using the LMS model. | (185–187) |

Abbreviations: DNT, dinitrotoluene; 2-AAF, 2-acetylaminofluorene; EGF, epidermal growth factor; BESTNOEL, biologically evaluated, scientifically tested no observed effect level; Ah, aryl hydrocarbon; LMS, linearized multistage.

[a]Not included in the table are examples of the use of qualitative experimental data in risk assessment, such as the use of evidence of genotoxic potential to buttress weight of evidence classifications of carcinogenic potential. The table is not intended to be an exhaustive compilation; a few pertinent examples are included that have not yet formally been applied in cancer risk assessments.

[b]Though this particular study was intended to demonstrate the use of this technique for immunotoxicological risk assessment, the general approach is also relevant to cancer risk assessment.

[c]This technique, known as the parallelogram approach, has been applied to estimate genetic risk to human germ line cells from data on mouse germ line cell mutation rates.

studies (*124,131,133*). Guidelines for conducting meta-analyses have recently been presented by a working group co-sponsored by the EPA (*129*). In Table 6, there are two examples illustrating productive uses of these techniques.

3. Verification of the plausibility of human risk estimates derived from animal data. Methods for using epidemiologic data in such a comparison have been well reviewed (*124,127,134,135*). Hertz-Picciotto (*127*) describes the process as including the following four steps: 1) conversion of human exposures to the units of exposure in the animal study; 2) application of the calculated unit risk to the doses received by the populations studied; 3) adjustment of cancer rates using a life-table analysis to account for the partial lifetime observed in the epidemiologic study; and 4) comparison of the numbers of deaths predicted from the animal study with those observed in the epidemiologic study. Two examples of the application of this procedure are shown in Table 6, in which comparison of human risk estimates calculated from rodent bioassay data for either ethylene dibromide (*136*) or methylene chloride

(*137*) and risks derived from human occupational studies were compared. In both of these studies, predictions of human risk based on results from the animal studies were significantly higher than risks observed in the epidemiologic studies.

4. Estimation of an upper limit of risk from negative epidemiologic data [reviewed by Wartenberg and Simon (*138*)]. This estimation should be a routine component in the analysis of any negative study. In the well-known example in Table 6, the statistical power of nine retrospective mortality studies of vinyl chloride workers were compared as a possible explanation for conflicting study results (*139*).

5. The use of dose–response models to estimate risk from epidemiologic data (*124,140,141*). Much less attention has been given to developing methods for quantitative risk assessment using epidemiologic data than has been given to models using animal bioassay data. There are, however, some examples in the published literature of the application to epidemiologic study results of both empirical and biologically based models developed for use with animal bioassay data; two examples are described in Table 6.

6. Using a "time window" type of analysis to define latency intervals. Shore and colleagues (*124,125*) have discussed the use of epidemiologic studies to refine the temporal projection of risk in several populations, such as cigarette smokers, asbestos workers, and populations exposed to radon, for which both exposure and disease information are available over an extended time period. The example in Table 6 involves a case–control occupational study of lung cancer among steel workers using years of employment in a high exposure area as a dose surrogate (*142*). Because exact latency for most cancers is not known, such analyses are often exploratory, but can be used to further explore consistency of results.

7. Molecular epidemiologic approaches. The use of nontumor response information in risk assessment emphasizing data from nonhuman or *in vitro* human sources was discussed above. In principle, any of the general approaches identified in Table 5 could be applied in humans. However, in addition to the data limitations discussed above, the application of some of the approaches in Table 5 to the *in vivo* human model is limited by ethical prohibitions against invasive experiments or the exposure of human subjects to potentially toxic agents. In spite of these difficulties, attempts are increasingly being made to integrate population-based epidemiology combining traditional clinical end points with molecular biological approaches [e.g., see Newman et al. (*143*)]. These efforts are uniquely valuable because they address aspects of the risk assessment paradigm that cannot be resolved using nonhuman experiments. Examples of two general approaches are provided in Table 6.

*EMF.* There are a number of characteristics of EMF, associated environmental exposure scenarios, and the current biological effects database that complicate the design of epidemiologic studies. These characteristics are briefly discussed below.

**Evidence of effect.** As reviewed above (see The Choice of an Appropriate Dose Metric), lack of knowledge of the relevant exposure (evidence of effect) makes epidemiologic studies difficult.

**Field characteristics.** In contrast to chemical agents, EMF are characterized by multiple parameters (see The Choice of an Appropriate Dose Metric) that may vary in relation to one another depending upon the exposure situation. Exposures in some occupational studies, particularly those involving electrical workers, are further complicated by the presence of transients and possible exposure to electric shocks. Thus, adequate characterization of actual EMF exposures of different individuals within a study population

**Table 6.** Uses of epidemiologic data in risk assessment[a]

| General approach | Examples | References |
|---|---|---|
| 1. To assist qualitatively in an overall weight of evidence hazard assessment by applying a range of weighting factors including quality and causal criteria | The inclusion of results of epidemiologic studies in the assignment of a potential carcinogenic agent to "known/likely," "cannot be determined," or "not likely" hazard classifications proposed by the EPA | (24) |
| 2. Using summary statistics from multiple individual studies, a pooled analysis with raw data, or other meta-analytic approaches to explore reasons and extent of heterogeneity | The use of pooled analysis with raw data from epidemiologic studies examining associations between mortality from cancer and monitored occupational radiation exposure | (188) |
| | Using summary statistics from multiple studies in a refutationist approach involving various regression techniques aimed at ruling out alternative noncausal explanations for observed associations between ethanol intake and risk of myocardial infarction | (151) |
| 3. To verify the plausibility of human risk estimates derived from animal data | Comparison of human risk estimates calculated from rodent bioassay data and human occupational studies for ethylene dibromide and methylene chloride | (136,137) |
| 4. To estimate the largest risk that could have gone undetected in a negative epidemiologic study | Comparison of the statistical power of nine retrospective mortality studies of vinyl chloride workers | (139,189) |
| 5. Estimating risk using dose–response models | The use of several different types of models to analyze the same retrospective cohort mortality study of lung cancer in workers exposed to cadmium | (140) |
| | The use of a variety of empirical linear and quadratic models to estimate risk from exposure to low levels of ionizing radiation | (65) |
| 6. Refining the temporal projection of risk to permit a more accurate projection of lifetime risk than afforded by a constant relative risk model | The use of "time windows" to determine when critical exposures eventually resulting in enhanced mortality due to lung cancer might have occurred in an occupational cohort | (125,142) |
| 7. Molecular epidemiologic approaches To assist in accounting for inter-individual differences in sensitivity to carcinogenesis by measuring enzyme activities or other physiological, biochemical, or molecular characteristics believed to be associated with carcinogenesis in accessible cells or tissues | | (38,190–192) |
| | The measurement of the activity of $O^6$-alkyldeoxyguanine-DNA alkyl transferase, a DNA repair enzyme | (193) |
| | The measurement of the inducibility of CYP1A1, an important enzyme involved both in the metabolic activation of many environmental carcinogens and in the binding efficiency of the Ah receptor | (46,194) |
| To provide a molecular dosimeter linking complex environmental exposures to internal events believed to be mechanistically involved in carcinogenesis. Such experiments may help to clarify an effective dose that may aid in establishing a truer indication of dose–response shape and potency than can be achieved using generalized external exposure measures | The measurement of biomarkers of PAHs in peripheral blood of children exposed to environmental pollutants | (195,196) |
| | The association of higher 4-aminobiphenyl hemoglobin adducts in smokers as compared to nonsmokers | (197) |

Abbreviations: Ah, aryl hydrocarbon; PAHs, polycyclic aromatic hydrocarbons.
[a]The uses listed are not intended to be exhaustive, but should illustrate the variety of ways in which epidemiology may inform a risk assessment.

may require complex multiparameter representations that are difficult to determine.

**Complex mixtures.** Exposures of human populations available for epidemiologic study such as electrical workers and residents living near power lines may involve not only EMF, which has been described as a complex mixture (89), but also environmental chemicals, radon, and in some cases ionizing radiation. Environmental exposures to chemical agents also commonly involve complex mixtures, which must be taken into account in study design.

**Ubiquity/multisource exposures.** All humans are exposed daily to low levels of EMF in virtually all aspects of their lives—residential, occupational, and recreational. This multisource exposure complicates the selection of control groups and the specification of total exposure.

**Weak potency of effect.** All biological effects of EMF that have been observed, both *in vivo* and *in vitro*, are quite weak, as are associations reported in epidemiologic studies. Epidemiologic studies may not be capable of distinguishing between weak associations and a null effect (144). And yet, because of the ubiquity of EMF, the presence of a weak association may be quite important from a public health point of view (135).

**Association with cancers for which other risk factors are unknown.** The cancers most often associated with EMF exposure are leukemia and brain cancer (2,44), two cancers for which the risk factors are mostly unknown. Thus, there is an insubstantial basis on which to control for potentially confounding factors such as lifestyles, dietary habits, or hereditary predispositions in epidemiologic studies.

**Exposure misclassification.** An unknown exposure metric, difficulties in exposure assessment, and other factors, lead to exposure misclassification, which could explain the lack of robust effects and inconsistencies among studies.

**Historical exposures.** Difficulties in measuring present day exposures are further exacerbated in attempting to estimate ubiquitous and unknown exposures from the past.

**Possible nonmonotonic dose response.** Though evidence is limited [see Bowman et al. (111) for discussion], so-called frequency or intensity "window" effects have been proposed for EMF. A nonmonotonic dose response would make the characterization of dose response using epidemiologic methods more difficult and would result in what might appear to be inconsistent epidemiologic results.

In determining which risk assessment techniques may be helpful in analyzing existing epidemiologic results and aiding in the design of future studies, the nine factors discussed above must be taken into account. For example, the uncertainty and lack of quantitative definition of dose response in the current epidemiologic database suggest that the application of quantitative models to calculate risk estimates would be inappropriate (1,2). Other uses of epidemiology are technically not yet feasible, such as molecular epidemiologic approaches.

However, some uses of the current EMF epidemiologic database in risk assessment appear to be well justified. First, epidemiologic study results should be an important part of a qualitative weight of evidence hazard assessment by applying various weighting factors including quality and causal criteria [e.g., see Kheifets and Kelsey (44)]. The factors discussed above, particularly the difficulty in measuring critical exposure parameters and the likelihood of

weak associations, detract from the ability of epidemiologic investigations to definitively establish a positive or a null effect. Thus, while epidemiologic studies appropriately play an important role in hazard identification aimed at establishing the presence of a potent effect, a hazard identification aimed at establishing the possibility of weak or null effects should assign significant weight to results of animal studies and other *in vivo* and *in vitro* sources of information as well as to results of epidemiologic studies.

Second, appropriate use of meta-analytic techniques should be very helpful in the analysis of the very large database of epidemiologic results for EMF. In fact, a number of meta-analyses have been performed using data from epidemiologic studies of EMF effects (*2,145–150*). For example, the NRC report on possible health effects of residential exposure to electric and magnetic fields included an assessment of the association between residential magnetic fields and childhood leukemia using the techniques of meta-analysis and concluded that the results for wire-codes were more consistent than those for measured fields (*2*). Washburn et al. (*149*) performed an analysis across 13 epidemiologic studies that examined associations between residential proximity to power lines and childhood leukemia, lymphoma, and nervous system tumors. Kheifets and colleagues used meta-analytic techniques to explore sources of heterogeneity across a large number of critically reviewed occupational studies that examined associations between central nervous system cancers (*147*) or leukemia (*148*) and occupational exposure to EMF. All studies point to uncertainties concerning exposure, bias, and potentially confounding factors, as well as issues of varying study quality or heterogeneity that prevent definitive conclusions. Thus, while such efforts may have been helpful in organizing results and conducting critical reviews, they have not resolved with certainty questions of potential risk from exposure to EMF. It may be useful to consider to what extent other meta-analytic approaches, such as a "refutationist" approach (*151*) (see Table 6), might be applicable to the EMF database.

Third, when results of ongoing animal cancer tests of EMF become available, it should be possible to use these results and the existing epidemiologic database to provide a rough indication of whether the results observed in the animal studies are consistent with epidemiologic results. Such an analysis should examine both positive and negative studies, including a determination of the largest risk that could have gone undetected in negative studies.

## Conclusions and Recommendations

In this review we have taken a broad view of the subject matter of risk assessment. We have emphasized that while a risk assessment may include a quantitative estimate of risk, given the current scientific and regulatory environment, this may be the exception rather than the rule. A risk assessment may be as simple as a qualitative hazard assessment, with virtually no quantitative aspects; it may have some quantitative aspects such as an assessment of the comparability of results from animal bioassays and human epidemiologic studies or a consideration of the likely effect of species differences on potency; or it may have sophisticated quantitative aspects such as the use of multiple parameters in a biologically motivated dose–response model or an analysis of curve shape in the low dose region using biochemical nontumor response data. Which set of analyses a specific risk assessment package includes will depend on the nature of the available knowledge base relevant to the agent in question and also on the degree of public or regulatory interest in the agent. The main point we wish to make is that a risk assessment is not one procedure with one outcome. It is a complex of related activities, all of which inform an overall judgment as to health risk.

A second point especially relevant to EMF, given the current status of that database, is that risk assessment is not just concerned with positive results. The focus in risk assessment is certainly on positive data for agents clearly indicated to be carcinogenic, for example, as in the case of the known human carcinogens vinyl chloride and ionizing radiation. However, the database relevant to risk assessment for many agents, including EMF, is complex, consisting of a mixture of negative studies, poorly reproducible positive results, and weak positive results (e.g., Table 1). As we have discussed in this review, the importance of including all data (both positive and negative) in a risk assessment is being increasingly emphasized by agencies such as the EPA and expert committees such as the NRC Committee on Science and Judgment in Risk Assessment and the Congressional Commission on Risk Assessment and Risk Management.

It is therefore essential to fully understand the manner in which negative data may be used in risk assessment. Whereas virtually every calculation made with positive data can be made using negative data, provided the concept of dose is changed from effective dose (or some related measure) to highest dose tested or to a highest

potency not detected determined by taking the power of the assay into account, it is not necessarily appropriate to make every calculation possible using negative data. In fact, it would be highly inappropriate to make a number of them. However, some calculations are clearly indicated. For example, a comprehensive hazard assessment should include calculations comparing the EMF exposures tested in animal bioassays to human exposures. Following a basic principle of toxicology, a negative animal bioassay would generally be judged to be inadequate or limited unless the high end of the dose range tested substantially exceeded human exposures. Therefore, this calculation should be applied to all animal bioassays, whether the results are negative or positive, as a criterion of adequacy. In addition, when multiple studies of the same or similar type are available, a comprehensive weight of evidence hazard assessment should include a quantitative analysis aimed at examining the consistency of results among the studies. For example, depending upon the power of a negative study, it may or may not contradict another positive study.

Thus, because the EMF database is large and complex and consists of many negative or poorly reproducible positive results, risk analysis will require the establishment of rigorous and thoughtful approaches. Without such a well-organized effort to utilize the considerable information in this database in a rigorous and comprehensive manner in the context of risk assessment but not exceeding the limits of the experimental and theoretical database, it will not be possible to draw any definitive conclusions as to the carcinogenic potential of EMF or to define an efficient research agenda aimed at clarifying uncertainties.

The NRC Committee on Science and Judgment in Risk Assessment (*23*) recommended what they termed an iterative approach to risk assessment. This recommendation is consistent with the perspective we have taken in this review, although we use the term "iterative" in a somewhat broader sense than that used by the NRC committee. We intend the term to imply that strategies for EMF should take a broad view of risk assessment as a collection of associated activities, some of which may be appropriate to undertake given the current state of the EMF database, some of which may require additional research efforts prior to being undertaken, and some of which may simply be inappropriate. When there is a need to make regulatory decisions, as the EPA has pointed out (*24*), it may be difficult to fully apply these principles. However, in the case of EMF, despite

the large database of information on potential health effects, the process is still in some sense in a fact-finding mode. Thus, at this point, one risk assessment goal may simply be to assess the adequacy of the experimental database for the purposes of conducting a comprehensive hazard assessment. For example, in the absence of empirical justification for the selection of a default dose metric, risk assessment strategies for EMF may adopt an approach in which a small number of simple default measures related to areas of environmental concern are selected (such as applied time-average field strength) and the adequacy of the biological effects database for a hazard assessment using those dose metrics is assessed. The resulting hazard assessment could either be used as a basis for a risk assessment, which would help to define the risk range excluded from environmental concern based on the current testing matrix, or to define areas in which additional testing is desirable. Additionally, some aspects of the current database may also permit certain other risk assessment activities to be performed. Even if some calculations are not justified by the data, it may be appropriate to carry out certain other analytical procedures, such as calculations to compare results in animal bioassays and human epidemiologic studies or to compare EMF exposures in assays measuring nontumor and tumor end points.

While it is not our intent to select a risk assessment strategy for EMF, based on discussion in the text we offer several suggestions below that may help to guide a process aimed at developing such a strategy.

First, while epidemiologic studies appropriately play an important role in hazard identification aimed at establishing the presence of a potent effect, a hazard identification aimed at establishing the possibility of weak or null effects, such as may be associated with EMF at environmental exposures, may have to assign greater weight to results of animal studies and other *in vivo* and *in vitro* sources of information. Although animal cancer bioassays suffer from statistical limitations and issues of relevancy to humans must be considered in interpreting results of assays in nonhuman systems, the ability to conduct these studies under controlled laboratory conditions using a wide range of defined exposures makes them uniquely valuable.

Second, because of the possibility that children may be at greater risk than adults from exposure to EMF, we recommend that a default factor to account for possible age differences in sensitivity to carcinogenesis be included in an EMF risk assessment.

Third, current evidence does not justify the use of any dose–response extrapolation procedure in conjunction with an EMF risk assessment. The inclusion of such a procedure will require new experimental evidence of a dose–response effect on tumorigenesis or a cancer-related biological process, or a viable mechanistic hypothesis.

Fourth, it is likely that a plausible argument may be constructed, based primarily on the apparent lack of DNA reactivity of EMF, to justify the use of simple measures of potency that do not involve extrapolation below the experimentally observable range (Table 2) and risk characterization metrics such as the MOE (Table 3), as recommended by EPA for so-called nonlinear carcinogens.

Finally, the development of any risk assessment strategy for EMF should take into account the fact that the current climate of risk assessment is much less formulaic than in previous years. As we have emphasized in this review, there is a much greater openness on the part of agencies such as the EPA to accommodate new approaches and agent-specific methodology. The use of nontumor data is probably the most exciting recent development in risk assessment (Table 5). Consistent with the limitations of the EMF health effects database, it will be important to explore ways that such data might be incorporated into risk assessment strategies. Risk assessment is now much more research driven and, importantly, also research-driving than in the past. Thus, an iterative risk assessment strategy should include not only procedures aimed at summarizing existing information in a way that informs as to potential health risks but it should also include information that defines data gaps and research needs appropriate to a more complete assessment.

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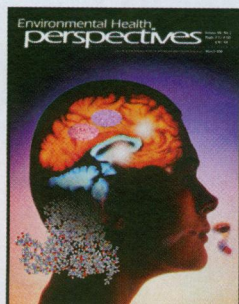
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